NDA 19-643/S-062, S-064

Merck & Co., Inc. 26 APR 2001
Attention: Michael C. Elia, Ph. D., DABT
Director, Regulatory Affairs
P. O. Box 4, BLA-20
West Point, PA 19486

Dear Dr. Elia:

Please refer to your supplemental new drug applications, S-062, dated June 29, 2000, received July 3, 2000, and S-064, dated November 7, 2000, received November 9, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Mevacor (lovastatin) Tablets.

We acknowledge receipt of your submissions dated February 27, April 17 and 26 (fax), 2001, for S-062.

The Change Being Effected supplemental new drug application, S-064, provides for revisions to the **WARNINGS**, *Skeletal Muscle* and **PRECAUTIONS**, *Drug Interactions*, subsections of the Package Insert. The following information has been added to these sections: "Although the data are insufficient for lovastatin, the risk of myopathy appears to be increased when verapamil is used concomitantly with a closely related HMG-CoA reductase inhibitor". In addition, "dermatomyositis" was added to the **ADVERSE REACTIONS**, *Hypersensitivity Reactions*, subsection of the Package Insert.

The supplemental new drug application, S-062, provides for revisions to the **CLINICAL PHARMACOLOGY**, *Pharmacokinetics* subsection. In addition, a new subsection "Geriatric Use" has been added to the **PRECAUTIONS** section of the Package Insert. The specific changes are as follows:

To the **CLINICAL PHARMACOLOGY**, *Pharmacokinetics* subsection, the following paragraph has been added:

> In a study including 16 elderly patients between 70-78 years of age who received MEVACOR 80 mg/day, the mean plasma level of HMG-CoA reductase inhibitory activity was increased approximately 45% compared with 18 patients between 18-30 years of age.
> (see PRECAUTIONS, *Geriatric Use*).

To the **PRECAUTIONS** section, the following paragraph has been added:

> *Geriatric Use*:
> A pharmacokinetic study with lovastatin showed the mean plasma level of HMG-CoA reductase inhibitory activity to be approximately 45% higher in elderly patients between 70-78 years of age compared with patients between 18-30 years of age; however, clinical study experience in the elderly indicates that dosage adjustment based on this age-related pharmacokinetic difference is not needed. In the two large clinical studies conducted with lovastatin (EXCEL and AFCAPS/TexCAPS), 21% (3094/14850) of patients were ≥65 years of age. Lipid-lowering efficacy with lovastatin was at least as great in elderly patients compared with younger patients, and there were no overall differences in safety over the 20 to 80 mg/day dosage range (see CLINICAL PHARMACOLOGY).

We have completed the review of these supplemental applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, these supplemental applications are approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert submitted April 17, 2001). We acknowledge your April 26, 2001 commitment to implement the revised package insert by June 30, 2001.

Please submit the copies of final printed labeling (FPL) electronically to each application according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, these submissions should be designated "FPL for approved supplement NDA 19-643/S-062, S-064." Approval of these submissions by FDA is not required before the labeling is used.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Margaret Simoneau, R.Ph., Regulatory Project Manager, at (301) 827-6411.

Sincerely,

David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research